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Is there a role for continuous renal replacement therapies in patients with liver and renal failure?

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Is there a role for continuous renal replacement therapies in patients with liver and renal failure? Continuous renal replacement therapy (CRRT) has now been in use for more than a decade in the management of patients with combined renal and hepatic failure. CRRT remains the treatment of choice in this group of critically ill patients because of improved cardiovascular and intracranial stability when compared with conventional intermittent hemofiltration and/or dialysis and effective solute clearances when compared with forms of peritoneal dialysis. Over the last decade, the technique has evolved with the introduction of pumped CRRT circuits, using machines that can accurately regulate fluid balance, and the commercial introduction of bicarbonate-based or "lactate-free" substitution fluids and/or dialysates. Whether continuous dialysis or hemofiltration is the mode of treatment choice remains unanswered, with greater amino acid and ammonia losses during dialysis, whereas hemofiltration leads to increased middle molecule and cytokine removal when compared with dialysis, the latter mainly caused by membrane adsorption. Whether the improved cardiovascular stability observed during these techniques is due to the removal of inflammatory mediators or is related to cooling as a consequence of the technique remains to be determined.

Patients with hepatocellular failure, whether acute or chronic, characteristically have generalized changes in circulatory dynamics, which are characterized by an increased cardiac output with reduced systemic vascular resistance, with evidence of tissue hypoxia [1]. This shunting of blood through the tissues, with resultant tissue hypoxia, is greater in those patients with acute liver failure and can be assessed using an oxygen flux test [2]. Thus, these patients are prone to develop acute renal failure either because of acute tubular necrosis, usually secondary to renal ischemic injury [3], or hepatorenal failure, when the normal autoregulatory renal compensatory mechanisms to preserve renal perfusion have been reset [4]. In addition, patients may develop acute renal failure secondary to nephrotoxic drugs and may also have pre-existing renal glomerular and/or tubular disease related to their primary liver disease.

Key words: renal and hepatic failure, critical care, fluid balance, hepatocellular failure, acute renal failure.

RENAL REPLACEMENT MODALITY

When continuous forms of hemofiltration and dialysis were first introduced into the treatment of patients with combined hepatic and renal failure, spontaneous circuits were used [5]. Subsequently, these have generally been replaced by pumped continuous renal replacement therapy (CRRT) circuits so that the CRRT circuit is no longer dependent on the mean arterial pressure, which is usually reduced despite vasoconstrictor requirement [6]. Compared with peritoneal dialysis, CRRT provides improved clearances and has a more predictable fluid balance [7]. Although the relative rate of solute clearance is greater during conventional intermittent hemodialysis, the absolute daily clearance is greater for CRRT, provided the circuit functions throughout the day [7]. More recently, slow overnight dialysis has been introduced using conventional dialysis equipment, but with reduced blood flows and dialysate flows, and can achieve similar clearances to CRRT.

Cardiovascular stability

One of the advantages reported by the pioneers of CRRT was improved cardiovascular stability and the ability to treat patients who otherwise would have been considered too unstable for conventional hemodialysis. However, over the past decade, there have been many technological advances in hemodialysis for patients with acute renal failure, including the introduction of daily treatments with the use of biocompatible membranes, priming the dialyzer and lines with albumin, high sodium dialysate concentrations, cooling the dialysate and the ability to continuously monitor plasma volume during treatment. Despite these measures, patients with cardiovascular instability, typified by those with acute hepatic failure, remain a group who can be problematic to dialyze

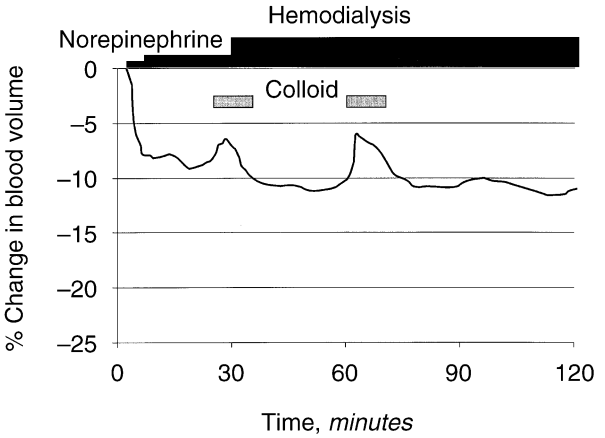

Fig. 1. Continuous blood volume measurement during conventional intermittent hemodialysis, set at an ultrafiltration rate of 100 ml/hr, with a low-flux polysulfon dialyzer, blood pump speed 200 ml/min, dialysate sodium 145 mmol/liter, and cooled to temperature of 35°C. These changes in blood volume occurred despite boluses of colloid infusions and increasing pressor support with norepinephrine.

(Fig. 1). Typically these patients develop hypotension within the first few minutes of connection to the dialysis circuit [8] because of a reduction in systemic vascular resistance and the effective circulating blood volume [9].

Plasma nitric oxide concentrations are increased in patients with liver failure, and this may be due to defective endotoxin extraction by the liver. At the start of dialysis, patients with acute liver failure have a greater increase in plasma nitric oxide than those with chronic liver disease and a much larger increase when compared with stable chronic hemodialysis patients [9]. Patients with liver failure treated by CRRT show greater cardiovascular stability when compared with intermittent hemofiltration or hemodialysis when initially connected to the circuit and during treatment [8]. Stability was greatest with spontaneous CRRT, followed by pumped CRRT. This suggests that blood pump speed and the initial interaction between the patient's blood and the extracorporeal circuit are important factors in determining this vasodilatory hypotension. As those patients with the most labile cardiovascular responses and the most severe liver failure have almost undetectable plasma complement proteins, it is unlikely that dialyzer–complement interactions play a significant role [10].

Intracranial pressure

Although intracranial hypertension has been reported in patients with chronic liver failure, it is typically found in those with fulminant hepatic failure [1]. The shorter the time interval between the start of symptoms and the onset of encephalopathy, then the greater risk of cerebral edema. Originally, many patients with fulminant hepatic failure were reported as dying from intracranial hypertension with coning and cerebellar herniation. More recently, it has been shown that cerebral ischemia is the more common form of brain injury [11] and that cerebral hypoxia then leads to the development of cerebral edema [1]. Thus, it is important in those patients who have lost cerebral autoregulation that both cerebral hypoxia and hypotensive episodes are avoided.

Typically, intermittent hemodialysis results in an increase in intracranial pressure, even in stable chronic dialysis patients. Within the first hour of dialysis, there is a significant detectable fall in the serum osmolality, and this may lead to the movement of plasma water into the extracellular and intracellular spaces because of the concentration gradient. In addition, hypotensive episodes or a net reduction in the effective circulating volume may result in cerebral hypoxia and the production of so-called idiogenic osmoles, thus increasing the concentration gradient and the backflow of water into the brain tissue [12]. In patients with acute liver failure, surges of intracranial pressure during intermittent hemofiltration and/or dialysis were typically detected both within the first hour and then toward the end of the treatment session. This suggests that changes in cerebral perfusion and cerebral hypoxia were the most important factors in determining cerebral stability [10]. Peritoneal dialysis has been reported to not adversely affect the intracranial pressure when used to manage acute renal failure in neurosurgical patients. However, in liver failure patients, fluid balance may be problematical, as ultrafiltration depends on the peritoneal blood supply. Many of these patients have abnormal portal blood flow, and vasoconstrictive agents such as norepinephrine reduce gastrointestinal blood flow. In addition, sudden changes in vascular tone associated with peritoneal drainage (Fig. 2) may provoke cerebral hypoxia and lead to brain death.

The introduction of CRRT provided a technique to treat acute renal failure in patients with cardiovascular instability and cerebral edema. This allowed the survival of patients with raised intracranial pressure with acute liver failure, who otherwise would have died [13]. Although the most likely explanation for this increased intracranial stability was improved cardiovascular stability, compared with intermittent hemodialysis and/or filtration, the rate of change of plasma osmolality was much smaller [10]. In addition, it was anecdotally noted that some patients who had raised intracranial pressure prior to starting CRRT developed increased intracranial pressure following the discontinuation of CRRT while waiting transfer to theater for orthotopic liver transplantation, suggesting that CRRT may improve cerebral stability by removing a cardiodepressant or a vascular endothelial vasodilatory factor.

Electrolyte balance

When orthotopic liver transplantation was in its infancy, patient survival was limited, and thus, many pa-

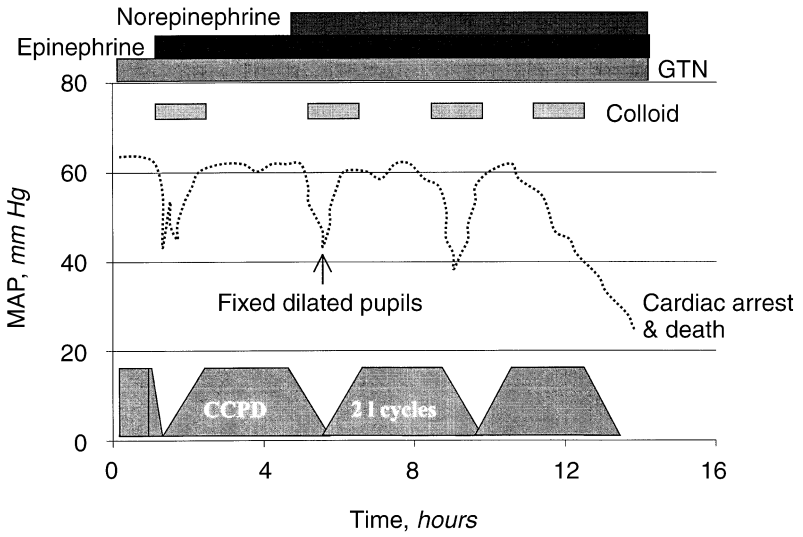

Fig. 2. Patient with renal failure and raised intracranial pressure treated by automated peritoneal dialysis. At each cycle exchange, there was a marked reduction in the mean arterial blood pressure, despite resuscitation attempts with colloid and increasing pressor doses, resulting in a fall in cerebral perfusion pressure and eventual death from brain ischemia.

tients referred with end-stage liver failure were severely hyponatremic. Several centers reported encephalopathy and even patient death caused by central pontine myelinosis caused by too rapid of a correction of the serum sodium as a consequence of transplantation [14]. We and others have successfully used CRRT to correct severe hyponatremia (serum sodium <120 mmol/liter) prior to liver transplantation [15]. The rate of rise of sodium is determined by both the rate of replacement fluid/dialysate flow and the sodium composition. At this controlled rate of increase, the serum sodium concentration can be normalized without the risk of pontine myelinosis.

Similarly, CRRT has proved effective in controlling postorthotopic liver transplantation electrolyte imbalances, typically hypernatremia, secondary to the sodium load from colloid infusions and sodium citrate in blood products, and hypercalcemia from repeated calcium administration.

Middle molecule clearance

Hemofiltration and hemodialysis essentially remove water soluble solutes. Although there have been reports of CRRT removing copper in cases of Wilson's disease [5], amino acids [16], and ammonia in fulminant hepatic failure [17, 18], the majority of patients died when treated by hemofiltration alone or in combination with other extracorporeal techniques, such as plasma exchange [18]. The amount of solutes removed depends on the technique used, being greater for hemodiafiltration than hemofiltration alone [16], and on both the plasma concentration [17] and the rate of dialysate flow/ultrafiltration rate [18]. Thus, although CRRT is very effective in maintaining circulatory, acid-base, and electrolyte balance in the anhepatic patient awaiting supraurgent transplantation [19], alone it is inadequate to maintain homeostasis in a patient with deteriorating hepatic function, and other bridges to hepatic transplantation are required [20].

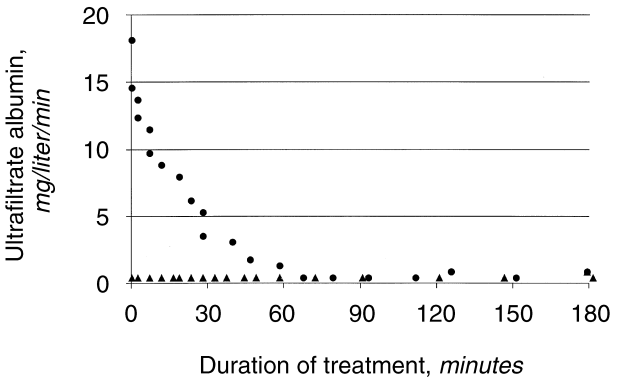

Fig. 3. Microalbumin losses in the ultrafiltrate during isovolemic venovenous hemofiltration, set at an ultrafiltration rate of 1000 ml/hr, using two similar surface area membranes, differing in their respective surface zeta (ζ) potentials (polyacrylonitrile very negative ζ potential). Symbols are: (●) polyamide; (▲) polyacrylonitrile.

Membrane bioincompatibility

There has been great interest in cytokine removal during CRRT. Patients with liver failure, possibly as a consequence of defective endotoxin removal, are known to have increased circulating levels of proinflammatory cytokines, particularly tumor necrosis factor-α. During CRRT, cytokine removal is mainly by membrane adsorption and is therefore greater during hemofiltration than hemodialysis [21]. Membrane adsorption depends on the negative membrane surface charge, known as the zeta (ζ) potential, the membrane surface area, and the blood flow rate. Membranes differ in their ζ potential, and this affects protein permeability and adsorption (Fig. 3). Thus, as expected, adsorption is maximal within the first

hour of treatment, whereas convective losses are relatively constant during treatment [21]. This suggests that there would be an advantage of regularly changing the CRRT hemofilter membrane to increase such adsorption losses.

Studies have suggested that both the initial cardiovascular and intracranial stability in patients with acute liver failure when starting hemofiltration may be affected by membrane bioincompatibility [8, 22]. This implies that some of the cardiovascular instability observed in these patients is due to increased endothelial dysfunction secondary to increased proinflammatory cytokines.

Anticoagulation

Most patients with fulminant hepatic failure are at increased risk of hemorrhage, with markedly abnormal throboelastographs, caused by a combination of clotting factor deficiencies, thrombocytopenia, and low-grade fibrinolysis with or without intravascular coagulation. Thus, many of these patients can be managed with anticoagulation-free CRRT circuits, especially if predilution fluid replacement is used [23]. However, some patients frequently clot their circuits. This is not thought to be due to activation of the traditional extrinsic coagulation cascade [23, 24] but due to increased activity of the intrinsic pathway, secondary to the release of tissue factor [24]. Endotoxemia activates endothelial cells and primes macrophages and other inflammatory cells to increase the release of tissue factor, thus increasing thrombin generation by the intrinsic pathway.

Anticoagulation with heparin may not be that effective in these patients because of reduced concentrations of antithrombin III and heparin cofactor II [23]. Similarly, citrate anticoagulation may potentially lead to citrate accumulation and metabolic alkalosis if the rate of citrate administration exceeds that of hepatic metabolism [25]. Others have used prostacyclin as an extracorporeal anticoagulant [26]. In patients with acute liver failure, prostacyclin has been reported to increase tissue oxygen uptake [1], not only peripherally [2], but also by the brain, and therefore, may help to prevent cerebral ischemic injury [11]. More recently, the serine protease inhibitors nafamostat maleate and kallikrein have been reported to be useful extracorporeal anticoagulants in these patients with hepatic failure [9, 23].

Anionic base

Traditionally, commercial hemofiltration substitution fluids/dialysates have either been lactate or acetate based. Patients with severe liver failure may be unable to adequately metabolize the lactate or acetate through to bicarbonate and thus may become more acidotic because of the continuous bicarbonate losses in the ultrafiltrate/dialysate [27]. More recently, bicarbonate-based or buffer-free solutions, in which bicarbonate has to be added in the venous return limb of the CRRT circuit, have been developed.

Compared with standard lactate-based solutions, we found that during the first day of CRRT, the average fall in arterial hydrogen ion concentration was 12 nmol/liter greater, and the total amount of anionic buffer administered was 225 mmol less when bicarbonate was used [28].

Thus, the commercial development of bicarbonate or buffer-free–based fluids should supersede lactate and acetate-based fluids.

SUMMARY

The development of CRRT in the management of acute renal failure in patients with both acute and chronic liver failure has been a major advance over the last decade. It allowed the treatment of patients who were cardiovascularly too unstable to tolerate conventional hemodialysis and provided excellent solute removal when compared with peritoneal dialysis. Although CRRT is not a substitute for a failing liver, it can be used to correct electrolyte imbalance prior to transplantation and to help maintain anhepatic patients that are awaiting urgent transplantation. Intraoperatively, CRRT is conventionally used during liver transplantation for those with acute liver failure and/or renal dysfunction prior to transplantation.

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